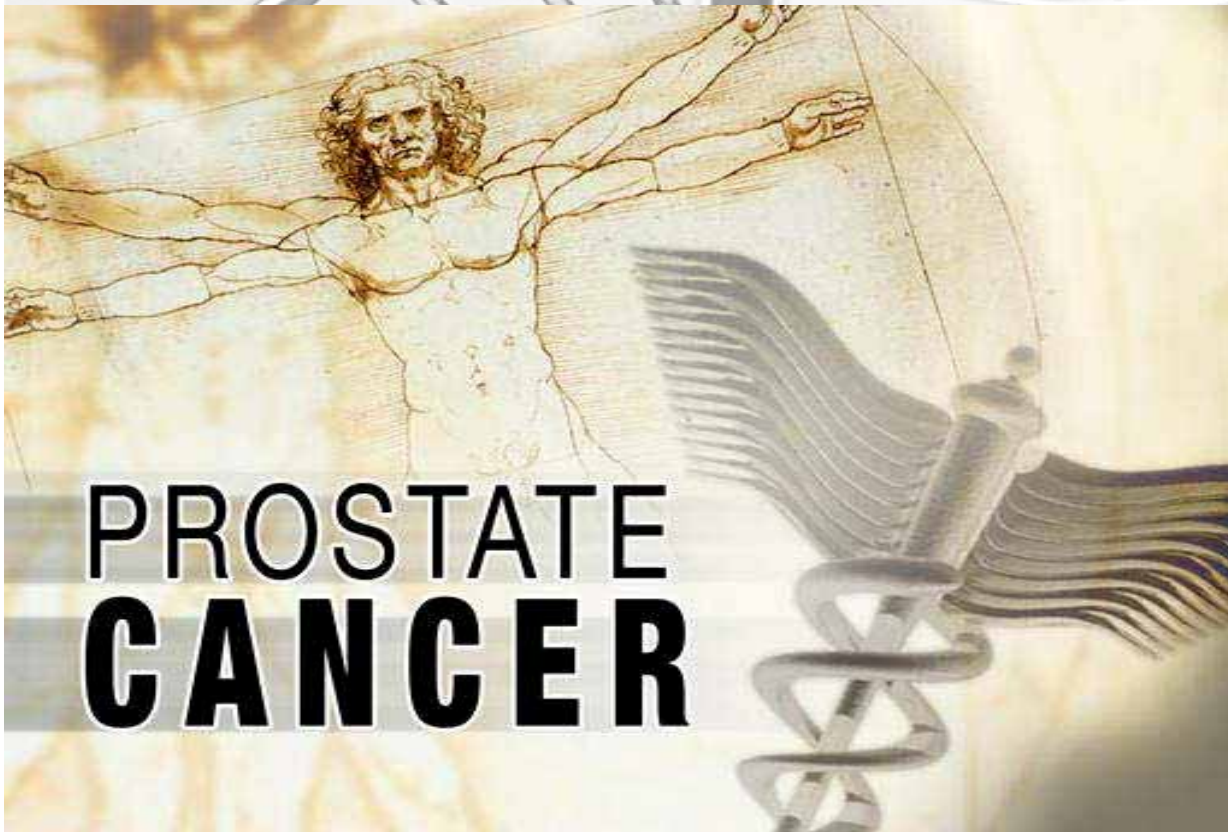


What are currently the best decision markers for biopsy and re-biopsy of the prostate?



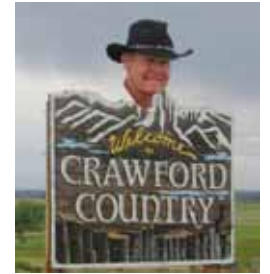
E. David Crawford,
M.D.



Professor of Surgery/
Urology/Radiation
Oncology

University of Colorado

Greetings from Colorado



Disclosures: Consultant: MDX Health, Myriad and Genomic Health

What are currently the best decision markers for biopsy and re-biopsy of the prostate?

- Answer: Markers which help determine which men have a cancer that would benefit from treatment.

- Outline:

Defining the Challenge

Prostate Cancer Markers(PCMs)

Working with Family Practice Physicians

Implementing Change

Message from USPSTF And other organizations following the lead

- PSA screening is a “D” recommendation
- Physicians should not order PSA screening unless they are prepared to engage in **shared decision making** that enables an informed choice by patients
- **What to do ?**

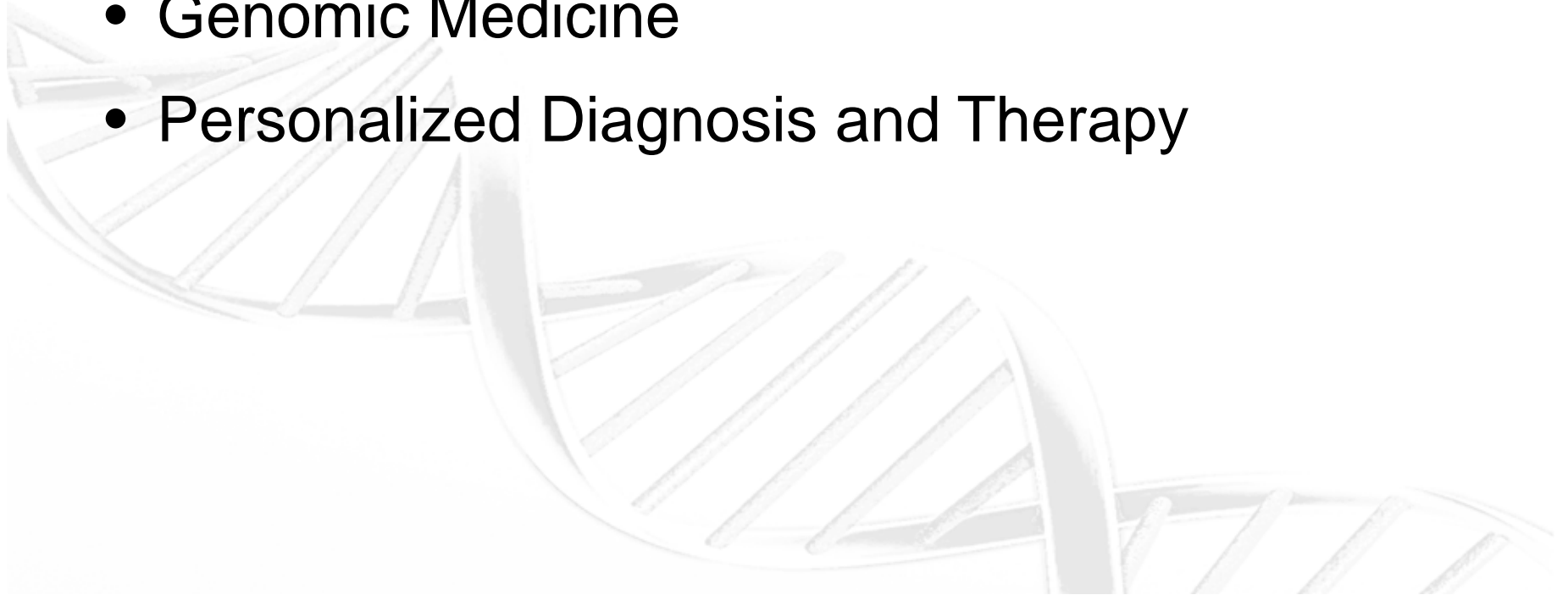
Prostate Cancer: Current Needs

- **Refine PSA**
- Increase the probability of an initial **positive biopsy**
- Reduce the number of **unnecessary repeat** biopsies by better distinguishing benign from malignant disease
- **Stratify** low risk from higher risk tumors
- Will **PCMs(Prostate Cancer Markers)** improve
the answer: Yes

Time for Change

Not one fits all

- Precision medicine
- Selection Medicine
- Stratifying medicine
- Genomic Medicine
- Personalized Diagnosis and Therapy



PCMs

Tissue

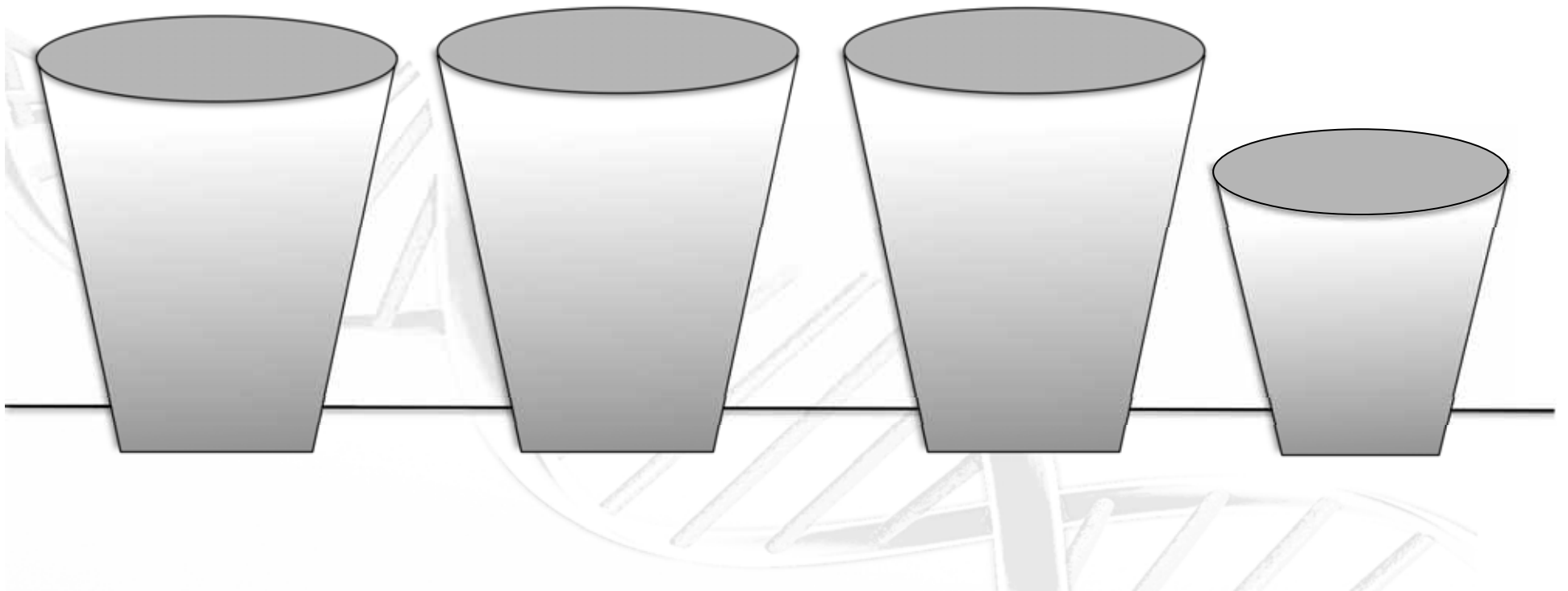
Blood

Urine

What is a biomarker?

A molecule that can be found in blood, tissue or body fluids that is a sign of a normal or abnormal process

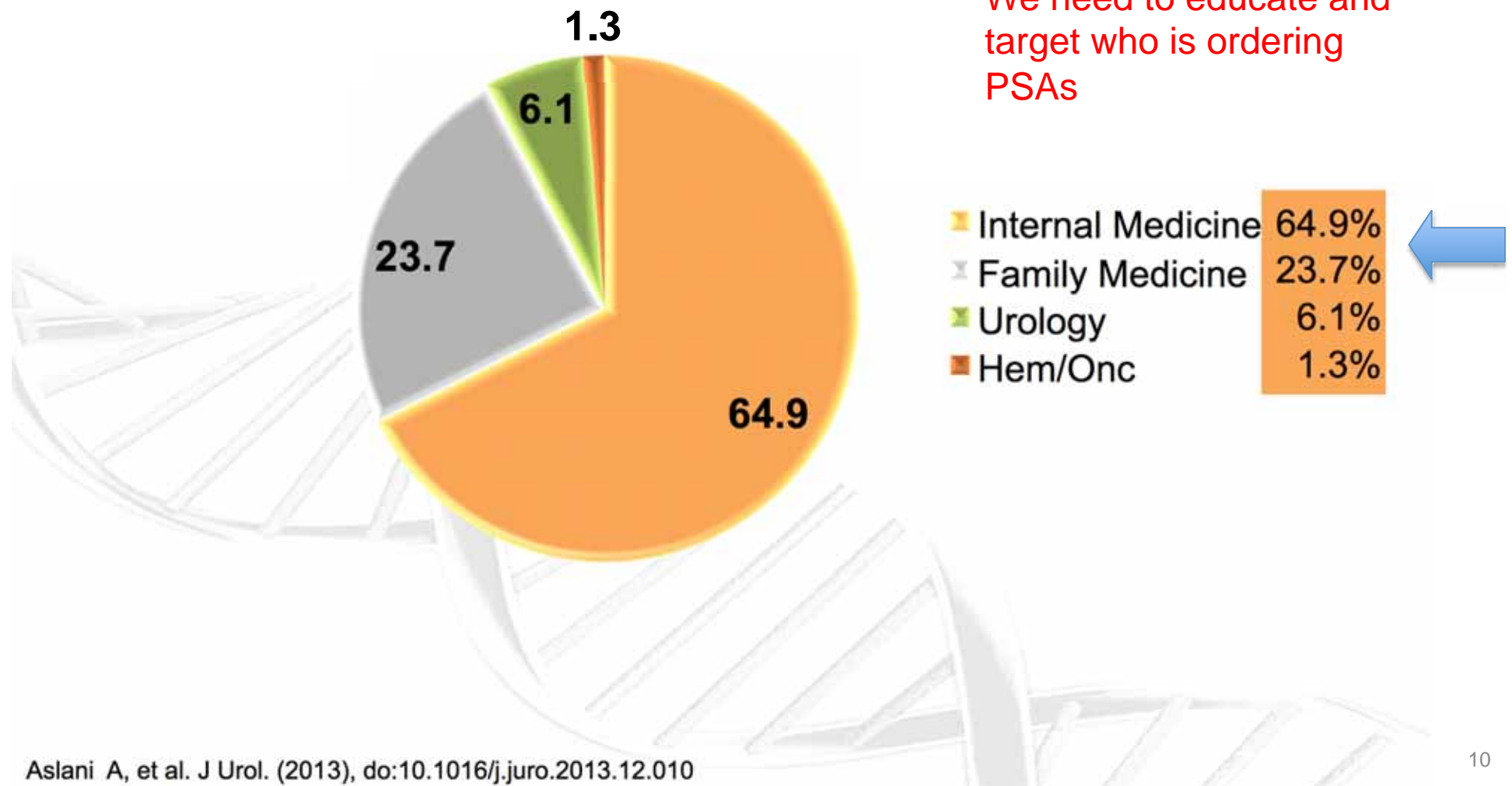
PCM Buckets



Ways Forward

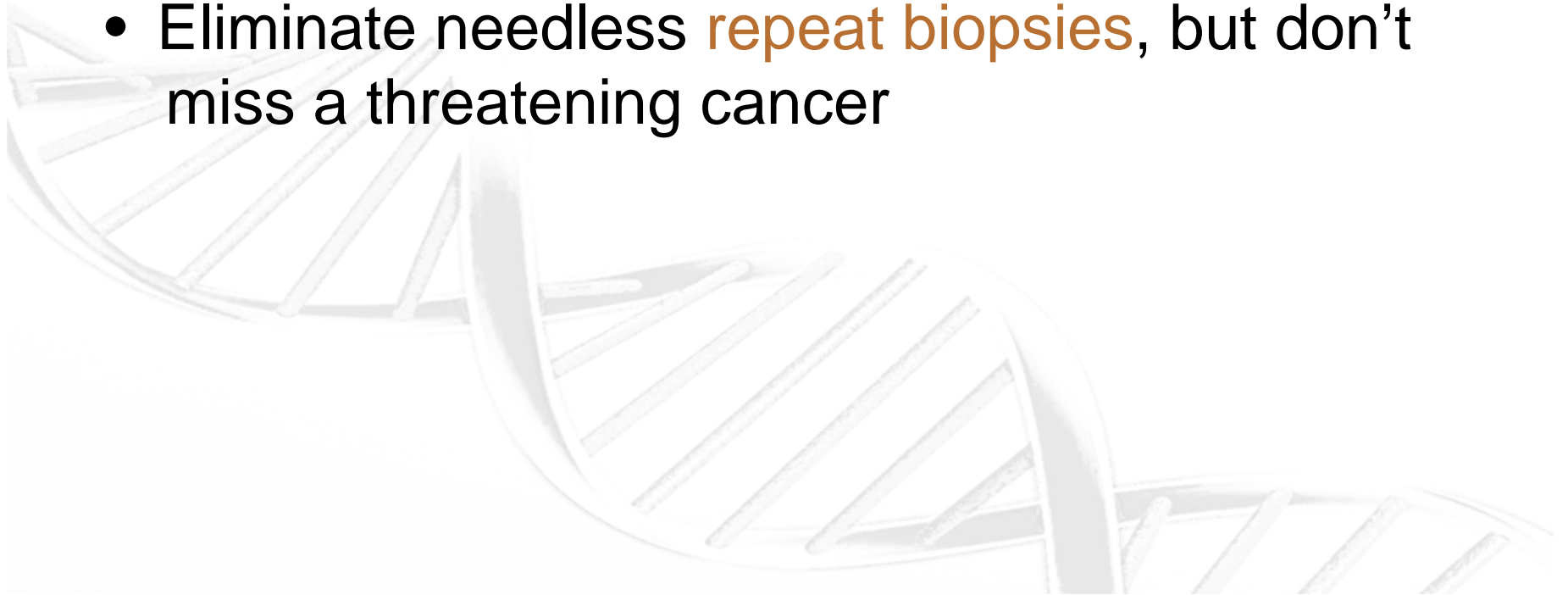
- Educate those who order PSAs-**Family Doctors**
- Define a **PSA level with little risk**
- Identify those who need further evaluation by a Urologist

Who is Ordering PSA Tests in United States?



Ways Forward

- **PSA Levels**
- Improving the **Performance** of the test and find cancers that **need to be treated**
- Eliminate needless **repeat biopsies**, but don't miss a threatening cancer



Defining PSA Levels and Improving Performance

Patients and Methods:

- 350,000 HMO-Henry Ford System
- Men in system 1997-2008
- Initial PSA between 1-5ng/ml
- Minimum 5 years follow-up
- No 5 ARIs

Results:

- Mean age -55 Mean PSA 1.0 African American 29%
 - Detected Cancer: 2%
- 21, 502 men eligible

What is the Appropriate PSA Level?

BJUI Prostate-specific antigen 1.5–4.0 ng/mL: a diagnostic challenge and danger zone

E. David Crawford, Judd W. Moul*, Kyle O. Rove, Curtis A. Pettaway†, Lois E. Lamerato* and Alexa Hughes

*University of Colorado, Anschutz Medical Campus, Aurora, CO, *Division of Urologic Surgery, Duke University Medical Center, Durham, NC, †MD Anderson Cancer Center, University of Texas, Houston, TX, and †Josephine Ford Cancer Center, Henry Ford Medical Center, Detroit, MI, USA*

Accepted for publication 20 January 2011

BJU Best Clinical Paper


UROLOGY NEWS: w treatment for prostate cancer... Use of ultrasound in patients with CKD...


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Uroscan
BJUI awards three 'Best Paper' prizes

 The Bob Krane Prize, awarded for the best clinical paper goes to E. David Crawford, MD. His paper points to a PSA threshold of 1.5 ng/mL as a potential danger zone when it comes to predicting an increased risk for prostate cancer over a 4-year period.

 The John Blandy Prize is awarded to the best paper published by a resident. Guillaume Ploussard was given the prize for five papers that were published during 2011 alone.

 The Coffey Prize rewards the best research paper. This year's winner, Tarek A Bismar, MD, sheds light on the importance of ERG gene rearrangements and PTEN genomic deletions in the development and progression of prostate cancer.

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5-year Diagnosis Rates Based on Initial PSA Level

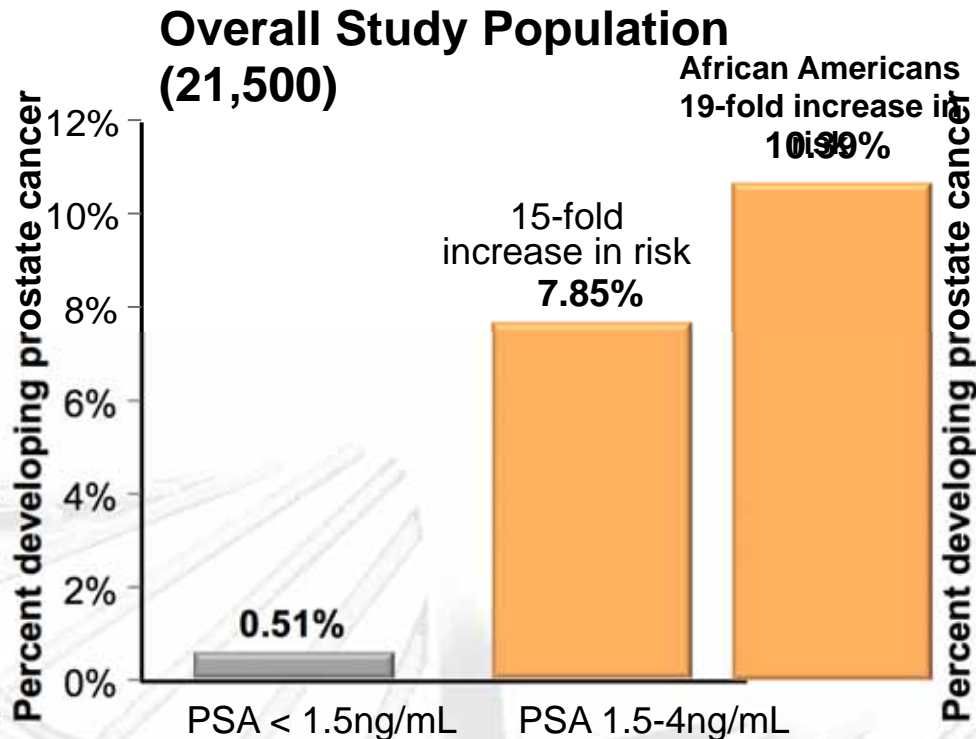
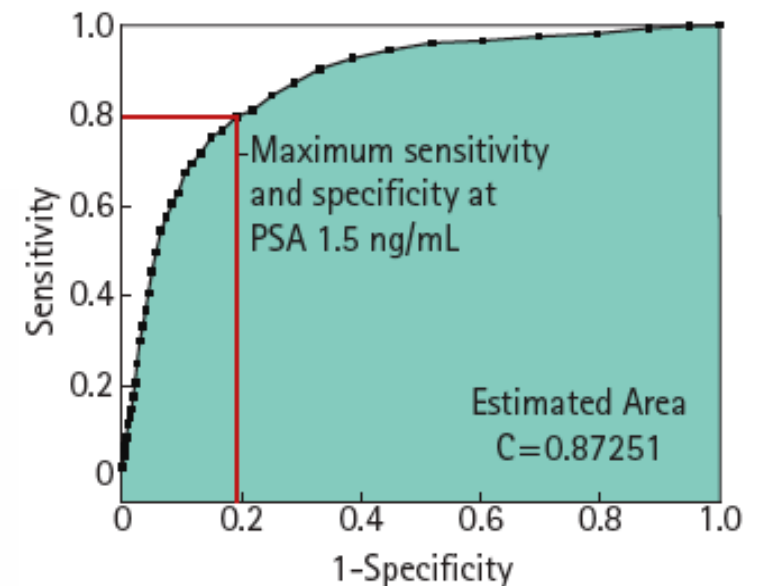


FIG. 2. Receiver operating characteristic curve for all patients.



A first PSA test threshold of 1.5 - 4.0 ng/mL, represents the Early-Warning PSA Zone
Patients with PSA \geq 1.5 ng/mL have an increased risk of developing PC

Early Detection A Way Forward

- PSA **treated like other lab tests**, lipids, electrolytes, weight, and BP-**Routine**
- Informed decision when tests **are abnormal**
- **70%** of men require **no discussion-based on our screening data on 150,000 men.**
- Men's Health broader issue $> 1.5\text{ng/ml}$ surrogate for BPH, Prostatitis, Prostate cancer.

Early Detection A Way Forward

- PSA Levels- > 1.5 ng/ml-Evaluate
- Improving the **Performance** of the test and find cancers that **need to be treated**

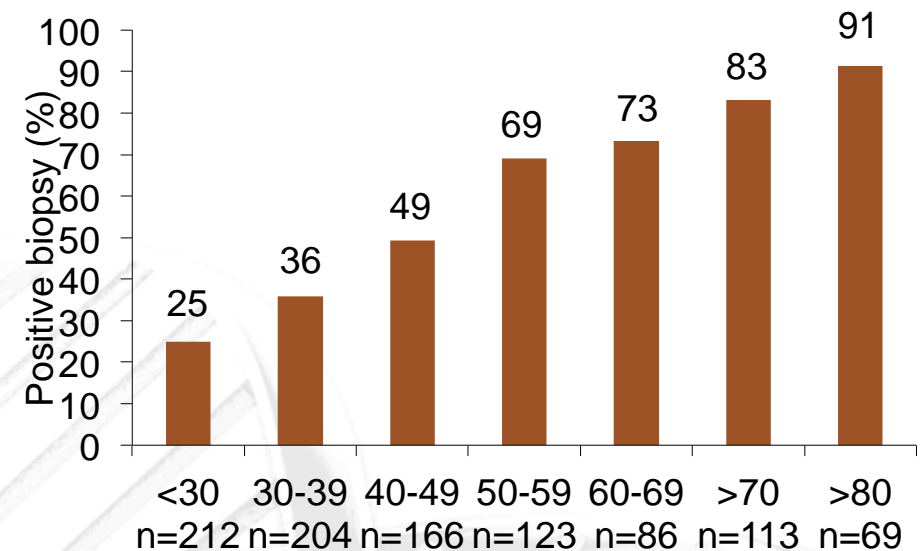
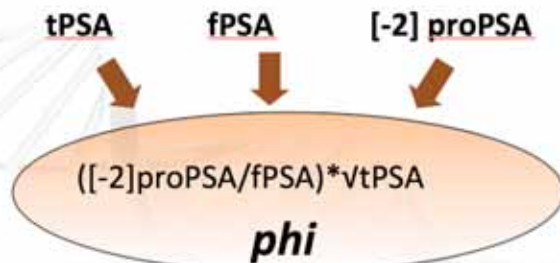


PSA Performance

PSA Isoforms

- Beckman Coulter *phi*
- For men with tPSA between 2–10 ng/mL and non suspicious DRE for PCa

- Beckman Coulter *phi*
- For men with tPSA between 2–10 ng/mL and non suspicious DRE for PCa



phi score

PSA

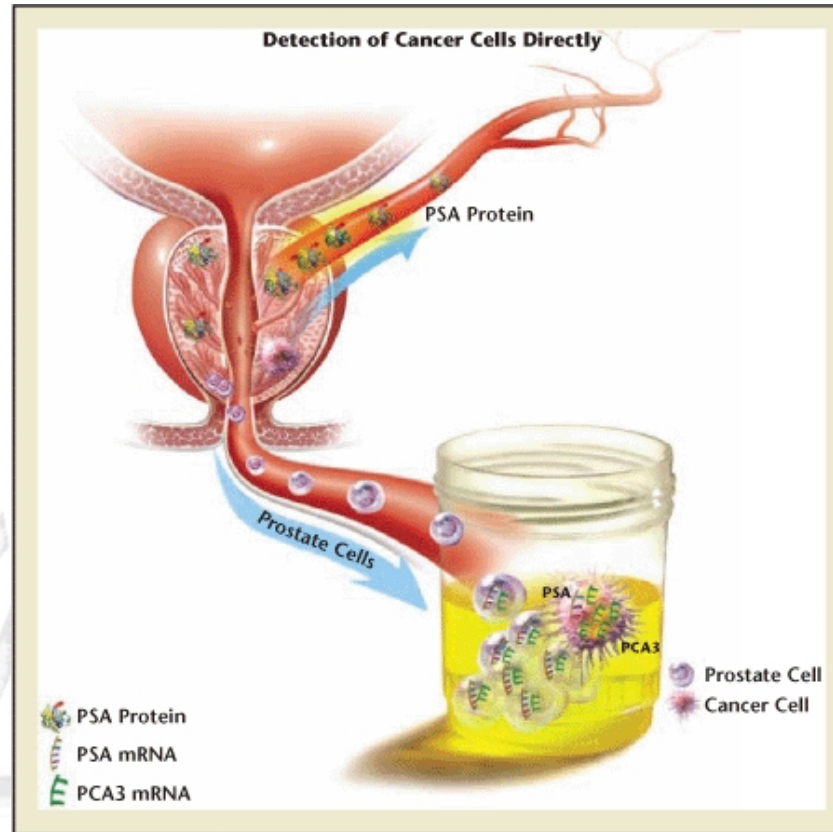
PCA3 score

prostate tumor
↓
marker release
from tumor

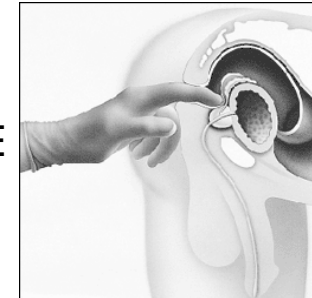


blood sample

Measure PSA
protein in serum



DRE



cell shedding ↓

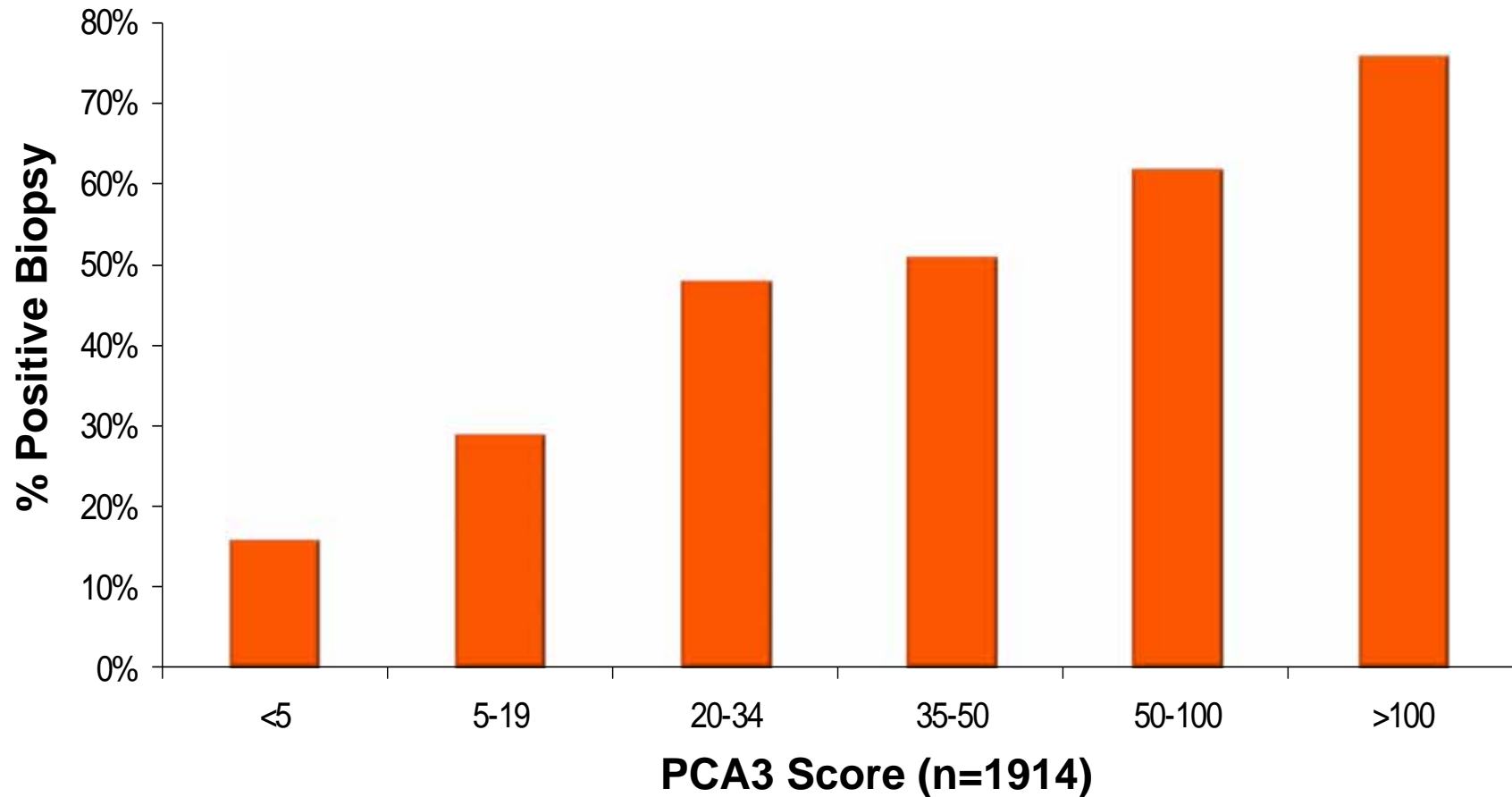


urine sample

Measure PCA3 and
PSA mRNA from cells

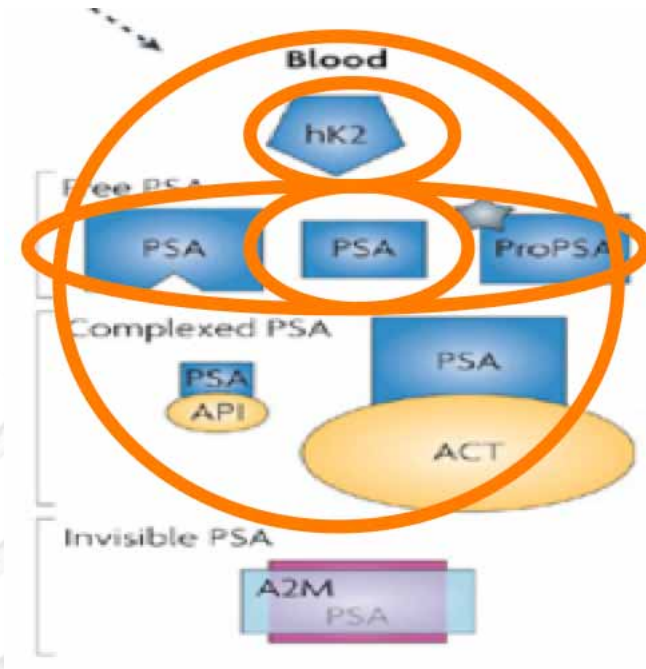
$$\text{PCA3 Score} = \text{PCA3/PSA mRNA} \times 10^{-3}$$

Percent of Men with Positive Biopsy by PCA3 Score First Biopsy



PSA PERFORMANCE 4Kscore

- **4Kscore™ Prostate Cancer Test**
- **Prostate cancer test**
- Based on the following panel of kallikrein markers:
 - Total PSA
 - Free PSA
 - Intact PSA
 - Human Kallikrein 2 (HK2)



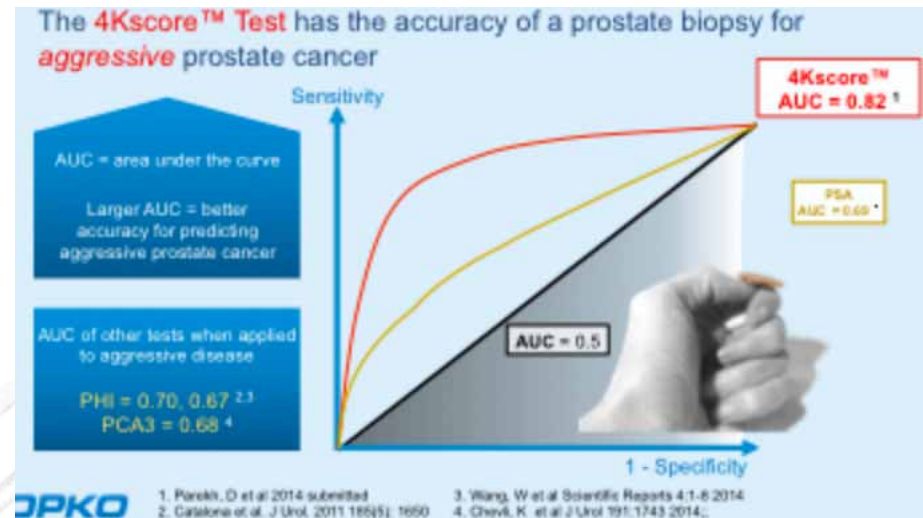
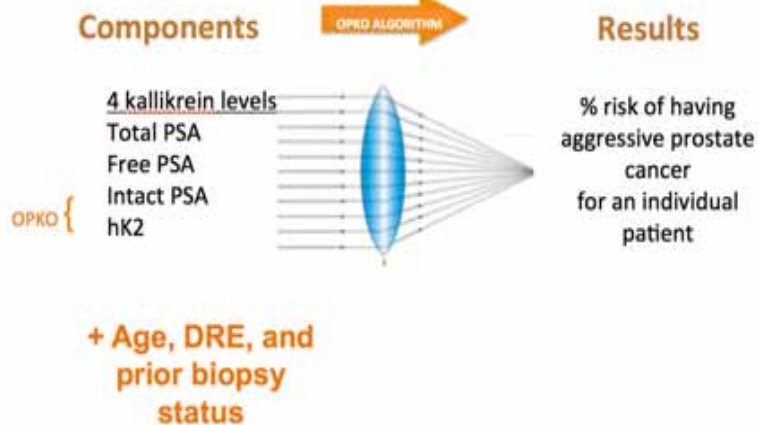
OPKO
OURlab

4K Score

Finding a **significant cancer**

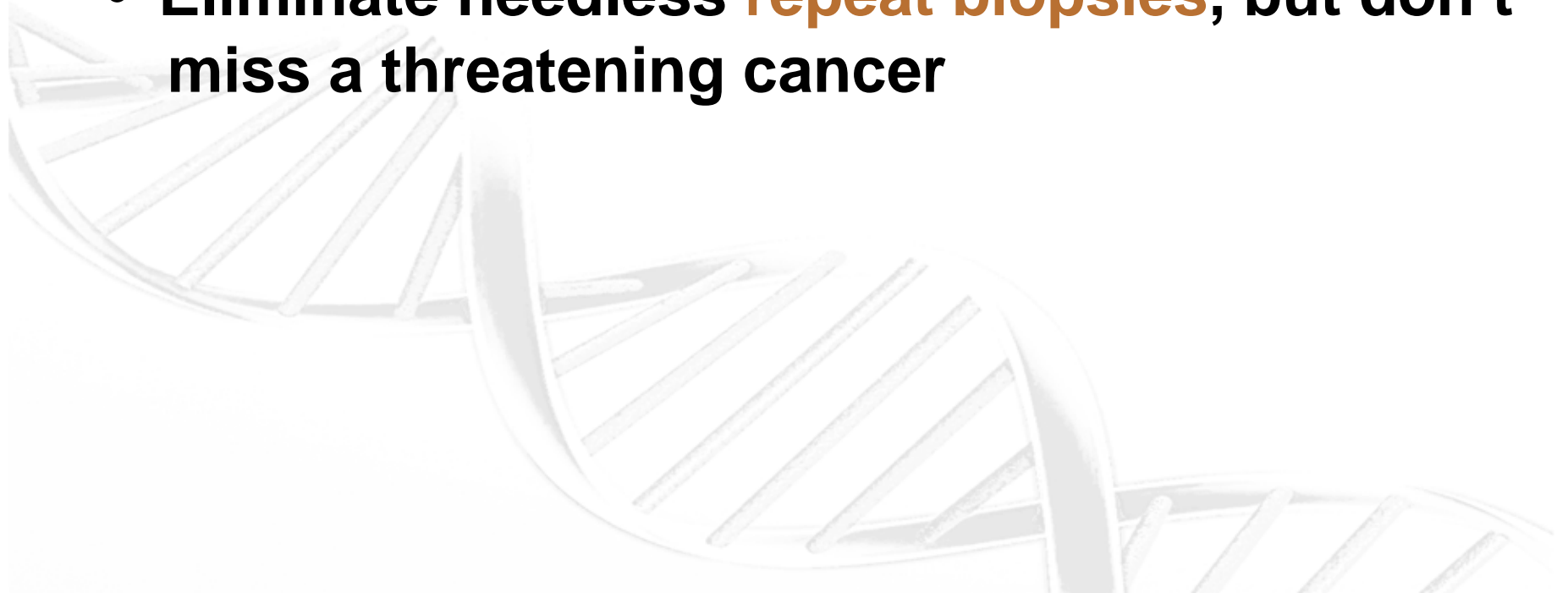
4 Kallikreins

Outperforms PSA



Ways Forward

- PSA Levels -1.5ng/ml
- Improving the Performance of the test and find cancers that need to be treated-PHI, PCA3, 4 K
- **Eliminate needless repeat biopsies, but don't miss a threatening cancer**



TRUS Biopsies

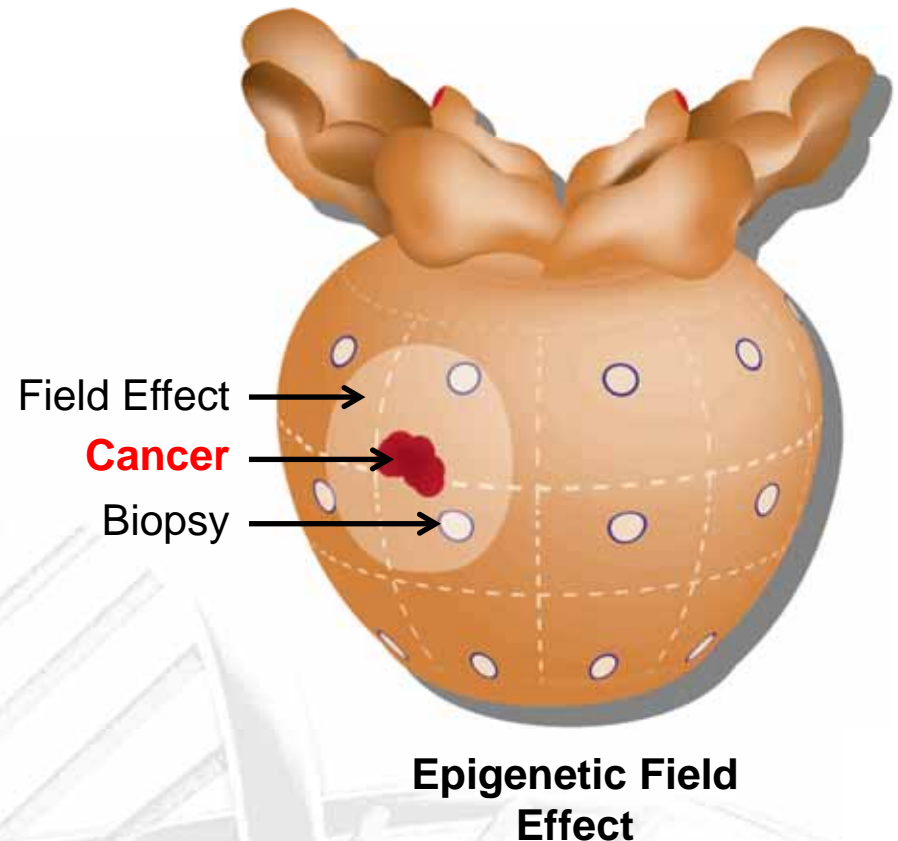
- Anxiety
- Repeat Biopsies
- Infections
- Miss Cancers

- Who to rebiopsy
- ConfirmMDX and PCA3

Improve Biopsy Outcomes Epigenetic Field Effect

ConfirmMDx detects an **epigenetic field** effect associated with the presence of cancer at the DNA level

- **Field effect** around a cancer lesion can be present despite normal appearance under the microscope
- **Absence of methylation** changes helps rule out malignancy
- **Presence of methylation** changes indicates increased risk for malignancy
 - **GSTP1** – DNA detoxification
 - **APC** – apoptosis
 - **RASSF1** – cell cycle regulation



Henrique R, et al., Epigenetic Heterogeneity of High-Grade Prostatic Intraepithelial Neoplasia: Clues for Clonal Progression in Prostate Carcinogenesis, Mol Cancer Res

Addressing False-Negative Biopsy Concerns

ConfirmMDx provides **actionable information** to improve patient risk stratification and decisions on repeat biopsy:

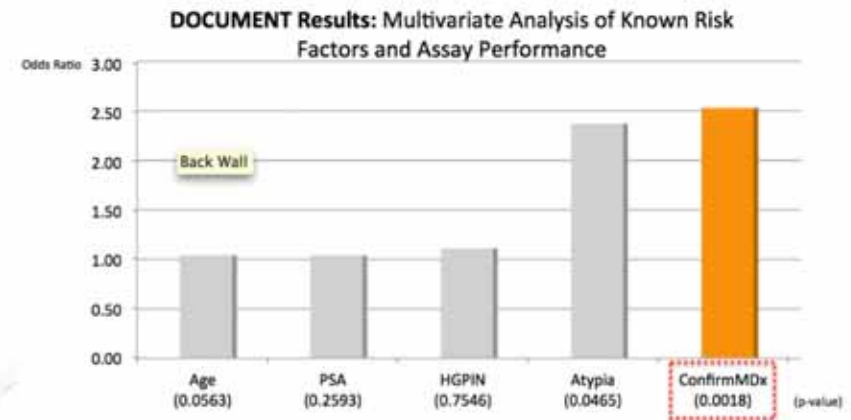
- ***RULE OUT*** prostate-cancer-free men from undergoing unnecessary repeat biopsies
- ***RULE IN*** those who require repeat biopsies and potential treatment

ConfirmMDx provides actionable information to improve patient risk stratification and decisions on repeat biopsy

Pivotal Trial: Second Validation Study



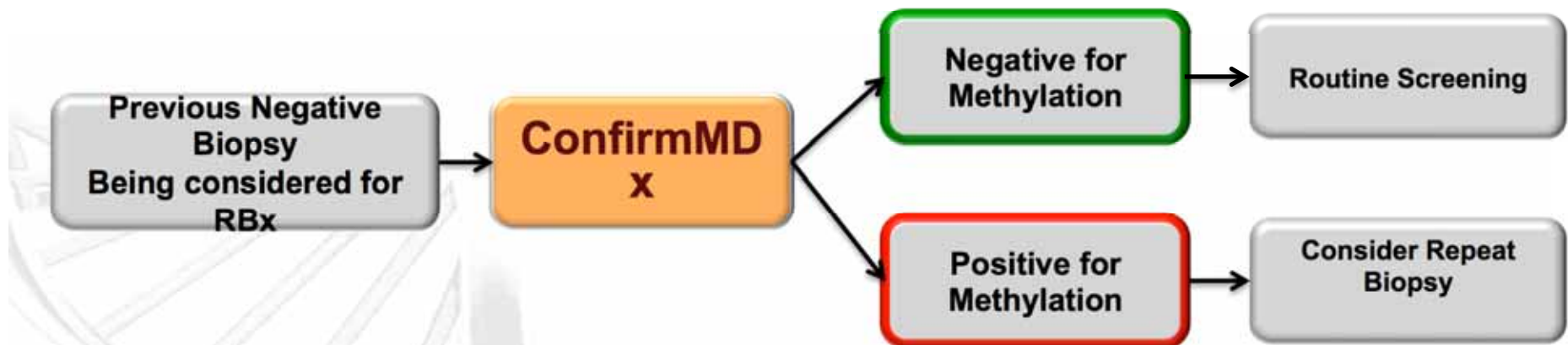
Document Clinical Trial



Partin et al; Clinical Validation of an Epigenetic Assay to Predict Negative Histopathological Results in Repeat Prostate Biopsies, *Journal of Urology* 2014. doi.org/10.1016/j.juro.2014.04.013

Where ConfirmMDx Fits

Patient Profile: Men considered for repeat prostate biopsy.



- Assay performed on residual tissue from previous negative biopsy
- Does not require repeat patient visit

